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THE DIAGNOSTIC AND PREDICTIVE ROLE OF NEUTROPHIL LYMPHOCYTES RATIO, D-NLR AND PLATELET LYMPHOCYTES RATIO IN COVID-19 PATIENTS

Respiratory Medicine

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ABSTRACT

Aim: To increase evidence that indicated the main role played by virus-triggered inflammation in the 2019novel coronavirus disease (COVID-19) which emerged in Wuhan City and rapidly spread throughout world.**Methods:** Age, neutrophil(NEU)-to-lymphocyte (LYM) ratio (NLR), lymphocyte-to-monocyte (MON) ratio, platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) of 93 patients with laboratory confirmed COVID19 were investigated and compared. The receiver operating characteristic curve was applied to determine the thresholds for five bio-markers, and their prognostic values were assessed via the Kaplan–Meier curve and multivariate COX regression models.
Results: The median age was 44 years old, and 35 cases were males. Fever (80.8%) and cough (71%) were the two most common symptoms. Elevated NLR and age were significantly associated with illness severity.
Conclusions: Elevated age and NLR can be considered independent biomarkers for indicating poor clinical outcomes.

KEYWORDS

1. INTRODUCTION

In December 2019, several cases of pneumonia of unknown etiology have been reported in China .On January 7, 2020, the Center for Disease Control and Prevention (CDC) has revealed a novel beta-coronavirus from the throat swab sample of a patient through high-throughput sequencing. Evidence suggest to the person-to-person transmission has occurred among close contacts in hospital and family. Inflammation is caused by infectious diseases, and growing evidence supports its significant role in the progression of various viral pneumonia. Hence,biomarkers that represent inflammation and immune status are potential predictors for the prognosis of COVID-19 patients. Peripheral white blood cell (WBC) count, neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), derived NLR ratio (d-NLR, neutrophil count divided by the result of WBC count minus neutrophil count), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) are indicators of the systematic inflammatory response that are widely investigated as useful.

	Total	Non-severe (n = 69)	Severe (including Critical illness) (n = 24)	Statistic test
Age (M ± SD)	46.4 ± 17.6	42.1 ± 18.6	57.9 ± 11.8	F = 4.65, P = 0.034
Sex (M/F)	56/37	38/31	18/6	χ^2 = 2.233, P = 0.135
WBC (M ± SD)	6.93 ± 3.9	6.4 ± 2.4	9.1 ± 5.6	F = 7.977, P = 0.006
LYM	1.04 ± 0.64	1.17 ± 0.63	0.65 ± 0.54	Z = −4.115, P < 0.001
NEU	5.38 ± 3.6	4.55 ± 0.21	7.73 ± 5.4	F = 13.18, P < 0.001
MON	0.43 ± 0.46	0.41 ± 0.2	0.5 ± 0.84	Z = −2.009, P = 0.045
NLR (M ± SD)	10.8 ± 15.6	4.8 ± 3.5	20.7 ± 24.1	Z = −4.798, P < 0.001
d-NLR (M ± SD)	5.07 ± 5.5	3.3 ± 1.9	9.8 ± 7.8	Z = −4.429, P < 0.001
LMR (M ± SD)	3.42 ± 4.6	4.1 ± 6.0	2.1 ± 1.6	Z = −3.306, P = 0.001
PLR (M ± SD)	255.8 ± 226.1	176.7 ± 84.2	436.5 ± 329.2	Z = −3.992, P < 0.001
CRP (M ± SD)	33.8 ± 48.4	20.1 ± 24.5	53.9 ± 60.1	Z = −3.012, P = 0.003
Wuhan exposure (%)	26 (27.8)	18 (26.1)	8 (33.3)	χ^2 = 0.957, p = 0.328
Co morbidities (%)	50 (53.7)	29 (42.1)	21 (87.5)	χ^2 = 14.8, p < 0.01
Diabetes	21 (22.5)	8 (11.6)	13 (54.2)	χ^2 = 16.7, p < 0.01
Hypertension	23 (24.7)	7 (10.1)	16 (66.8)	χ^2 = 30.6, p < 0.01
hepatitis B	11 (11.8)	7 (10.1)	4 (16.7)	χ^2 = 0.628, p = 0.409
Heart disease	13 (13.9)	4 (5.8)	9 (37.5)	χ^2 = 14.9, p < 0.01
Renal dysfunction	10 (10.7)	2 (2.9)	8 (33.3)	χ^2 = 17.2, p < 0.01
Abnormal liver function	13 (13.9)	9 (13.0)	4 (16.7)	χ^2 = 0.194, p = 0.659
others	5 (5.4)	3 (4.3)	2 (8.3)	χ^2 = 0.556, p = 0.456

By collecting the data from 93 laboratory-confirmed cases, we attempted to determine the effect of sex, age, CRP, WBC count, NLR, LMR, PLR, and co morbidities on the length of stay of patients with COVID-19 pneumonia.

1. MATERIALS AND METHODS

2.1. Patients

We performed a retrospective study on the clinical characteristics of laboratory confirmed cases with COVID-19. Patients with complete clinical data, including 70 non-severe and 23 severe cases, were randomly selected. Non-severe patients met all following conditions: (1) Epidemiology history, (2) Fever or other respiratory symptoms, (3) Typical CT image abnormities of viral pneumonia, and (4) Positive result of RT-PCR for SARS-CoV-2 RNA. Severe patients additionally met at least one of the following conditions: (1) Shortness of breath, RR ≥ 30 times/min, (2) Oxygen saturation (Resting state) ≤ 93%, (3) $PaO_2/FiO_2 \leq 300$ mmHg. Patients with COVID-19 were confirmed by a positive result from the highthroughput sequencing or real-time reverse transcriptase-polymerase chain reaction assay for nasal and pharyngeal swab specimen.

2.2. Clinical characteristics and laboratory data

Epidemiological characteristics, including recent exposure history, clinical symptoms and signs, and laboratory findings, were obtained from electronic medical records and telephone confirmation. Laboratory assessments consisted of complete blood count, blood chemistry and CRP. The severity of COVID-19 was defined on the basis of international guidelines for community-acquired pneumonia.

2.3. Statistical analysis

Continuous variables were expressed as the appropriate means and standard deviations or medians and interquartile ranges. Categorical variables were summarized as the counts and percentages in each category. We grouped the patients into severe and non-severe COVID-19 according to the interim guidance of the World Health Organization and diagnosis and treatment guidelines of COVID-19 which included the clinical management of severe acute respiratory infection in suspected cases. Wilcoxon rank sum tests were applied to continuous variables, and chi-square and Fisher's exact tests were used for categorical variables. The optimal cut-off values of the continuous NLR, d-NLR, PLR, and LMR were calculated by applying the receiver operating curve (ROC) analysis .Hazard risk (HR) and 95% confidence interval (CI) were used as common measures to assess relative risk. Enter elimination binary logistic regression analysis was conducted to determine the influence of age, gender, and all other significant factors. $P < 0.05$ was recognized as statistically significant.

2. RESULTS

3.1. Results of WBC count, NLR, LMR, PLR, CRP, d-NLR, and clinical characteristics in the study subjects

The demographics and clinical characteristics in the study subjects are shown in Table 1. The proportion of selected severe cases, including critical illness, was 25%. The average age was 48 years old, with 83 years old as the maximum. The average age of non-severe cases was 32 years old, with 7 months old as the minimum. The age, WBC count, NLR, LMR, PLR, CRP, and d-NLR of severe patients were significantly higher than those of non-severe patients. However, no significant difference was observed in terms of gender.

Fig. 1. ROC curve used to distinguish patients with severe and non-severe COVID-19.27.8% (26/93) and 73.1% (68/93), respectively. Fever (83.8%) and cough (67.7%) were the first and most common symptoms before admission. Lymphopenia and neutrophilia were observed in 80.6% and 51.6% of patients, respectively. The laboratory reference values of LYM, NEU, and MON were 1.2–3.4, 1.8–6.3, and 0.1–0.6 E9/L, respectively.

3.2. Use of the optimum cut-off values of laboratory results to discern severe from non-severe COVID-19 infection

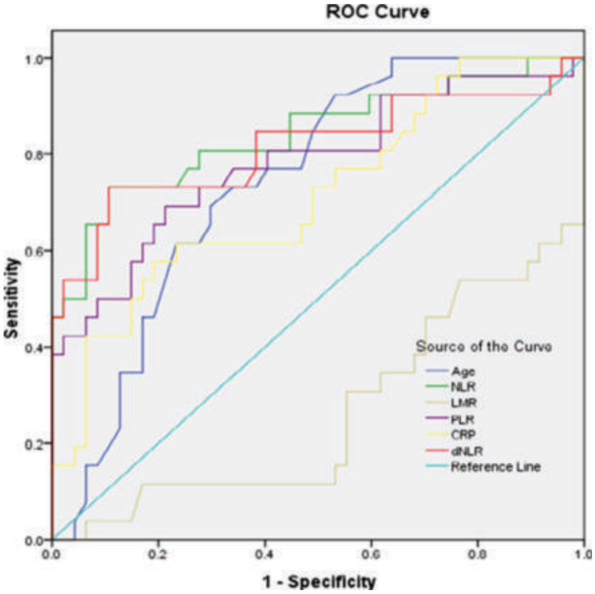

Fig. 1. ROC curve used to distinguish patients with severe and non-severe COVID-19.

3.2. Use of the optimum cut-off values of laboratory results to discern severe from non-severe COVID-19 infection Given that NLR, LMR, PLR, d-NLR, WBC count, and CRP were used to identify patients with severe or non-severe cases of COVID-19, patients with pneumonia were limited. No unified laboratory reference value was found. Therefore, we analyzed the optimal cut-off values calculated by the ROC analysis, and the ROC curves were presented in Fig. 1. In Fig. 1, areas under the curve (AUC) of age, NLR, d-NLR, CRP, LMR and PLR were 0.743, 0.841, 0.815, 0.714, 0.265, and 0.784. LMR could not be used as a potential diagnostic biomarker for subsequent analysis because its AUC was less than 0.50. The optimal cut-off values were 3.3, 2.8, and 180 for NLR, d-NLR, and PLR, respectively. The highest specificity and sensitivity were 0.636 and 0.88, 0.55 and 0.84, 0.44 and 0.77 for NLR, d-NLR, and PLR, respectively. The optimum cutoff values of age, WBC count, and CRP were 49.5 years, 7.2E9/L, and 20.3 mg/L, respectively (see Table 2).

Table 2 Areas under the curve (AUC) of age, NLR, d-NLR, PLR, CRP and LMR.

				Lower Bound	Upper Bound
Age	0.743	0.057	0.001	0.631	0.854
NLR	0.841	0.053	0.000	0.737	0.945
LMR	0.265	0.064	0.001	0.141	0.390
PLR	0.784	0.060	0.000	0.666	0.901
CRP	0.714	0.064	0.003	0.589	0.839
d-NLR	0.815	0.060	0.000	0.697	0.933

Test Result Area Std. Errora Asymptotic Sig.b Asymptotic 95% Variable(s) Confidence Interval

The test result variable(s): Age, NLR, LMR, PLR, CRP, d-NLR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

3.3. Kaplan–Meier curves of NLR, d-NLR, and PLR for determining the factors that affect COVID-19 progression

To identify the factors that affect COVID-19 progression, eight potential factors were included in the analysis by using the Kaplan–Meier curve and the univariate Cox regression model. Furthermore, age, sex, and the significant factors in univariate analysis were included to determine their influences on non-severe time further. Figs. 2, 3 and 4 showed that the evaluated NLR, d-NLR, and PLR had slight or significantly unfavorable NST, respectively. Evaluated NLR (HR 2.46, 95% CI 1.98–4.569), d-NLR (HR 1.92, 95% CI 0.817–3.496), and PLR (HR

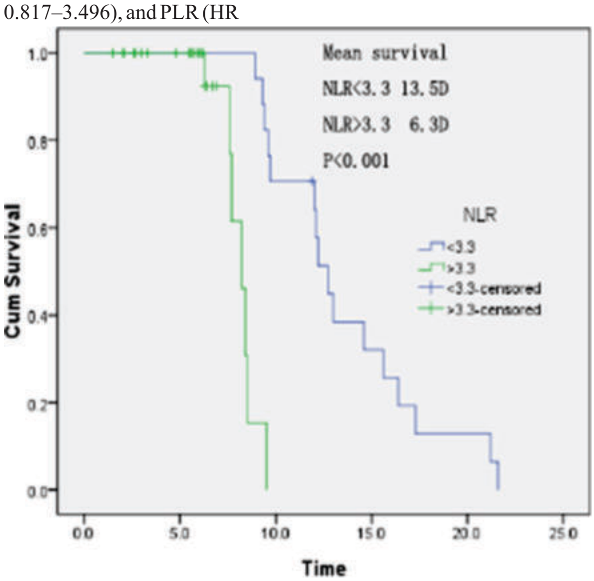

Fig. 2. Kaplan–Meier curves of NLR for non-sever of COVID-19.

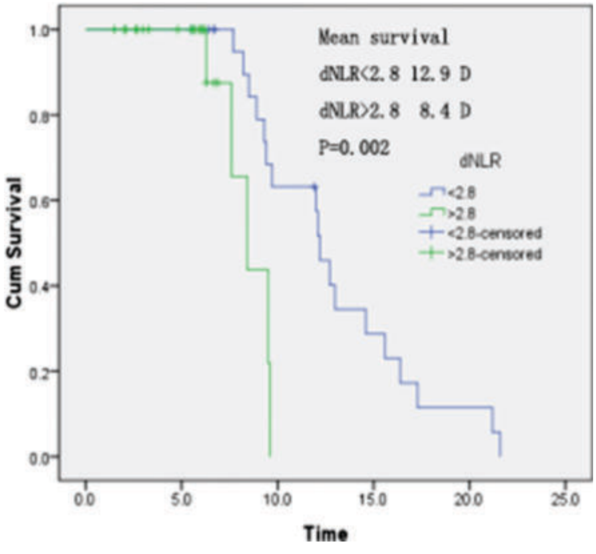

Fig. 3. Kaplan–Meier curves of d-NLR for non-sever of COVID-19.

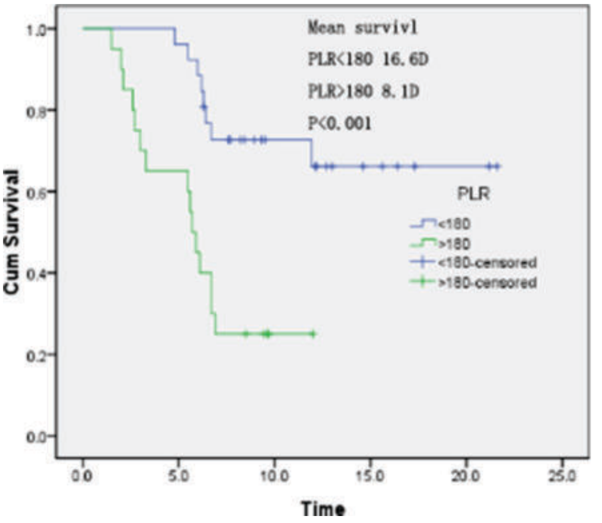

Fig. 4. Kaplan–Meier curves of PLR for non-sever of COVID-19.

1.023, 95% CI 0.921–1.756) identified by multivariate Cox regression were considered independent factors associated with COVID-19 progression.

3.4. Association of NLR, d-NLR, and PLR results with the risk of COVID-19 pneumonia

To identify the factors that may affect COVID-19 progression, we obtained the crude odds ratio (OR) after conducting the logistic regression analysis (Table 3).

Table 3 The OR and ORa in each of the NLR, d-NLR, PLR.

Indicators	Crude odds ratio (OR)	P	Adjusted odds ratio (ORa)*	P
WBC	1.223 (0.891–1.756)	0.132	1.118 (0.888–1.543)	0.146
CRP	1.323 (0.961–2.086)	0.109	1.206 (0.898–2.045)	0.138
PLR	1.023 (0.921–1.756)	0.166	1.018 (0.988–1.749)	0.252
d-NLR	1.932 (0.817–3.496)	0.134	1.901 (0.841–4.300)	0.123
NLR	2.462 (1.981–4.569)	0.044	2.886 (2.064–4.860)	0.019

Given that the blood test results were influenced by age and gender, we excluded the possible effects of age and gender and obtained the adjusted OR after the adjustment of gender and age. The results showed that NLR was positively correlated with the risk of COVID-19.

* Adjustment for age and gender.

1. DISCUSSION

COVID-19 has elicits a rapid spread of outbreak with the human-tohuman transmission, with a median incubation period of 7 days and a relatively low fatality rate. Mortality was less than 2.5%.In recent publications, the clinical characteristics of COVID-19 are similar to those of SARS-CoV. Fever and cough were the dominant symptoms, whereas gastrointestinal symptoms were rare. Fever occurred in only 43%of patients on initial presentation and developed in 83% after hospitalization. The absence of fever in COVID-19 was more frequent than in SARS-CoV (1%) and MERS-CoV infection (2%). lymphopenia is common and severe in some cases. Significantly high frequencies of severe cases were observed in elder patients with diabetes or hypertension (Table 1).

After the discussion of the clinical features of COVID-19, we analyzed the immunological characteristics of peripheral blood in patients with COVID-19. In the present study, our results first proved our hypothesis and indicated that elevated NLR was an independent prognostic biomarker that affected pneumonia progression in COVID-19 patients. On the one hand, neutrophil (NEU) is a major component of the leukocyte population that activates and migrates from the venous system to the immune organ or system. NEU releases large amounts of reactive oxygen species that can induce cell DNA damage and free the virus from the cells. Thus, antibody dependent cell mediated cell (ADCC) may kill the virus directly, expose virus antigen, and stimulate cell-specific and humoral immunities.

In our study, the applicable thresholds for NLR, d-NLR, PLR, and LMR were observed using the ROC curve. The optimal threshold at 3.0 for NLR showed a superior prognostic possibility of clinical symptoms to change from mild to severe, which had the highest of sensitivity and specificity and the largest of AUC. Finally, the findings of this study indicated that elevated NLR was an independent prognostic biomarker for COVID-19 patients.

In conclusion, The COVID-19 epidemic spread rapidly by human-to-human. The clinical manifestations of this disease can vary even in patients with the same viral infection. The conclusions of this study support that elevated NLR is an independent prognostic biomarker for COVID-19 patients.

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